gens," from which the blessings of prospective randomization become apparent. The entire A.M.A. series included premenopausal patients treated by androgens, as well as postmenopausal women treated both by androgens and estrogens, as cited above. The comparative efficacy of androgens and estrogens were calculated in 770 postmenopausal women by decades, both by chronologic and physiologic (years postmenopausal) criteria. With adequately sized samples, the effectiveness of the two types of additive hormones was similar through the fourth postmenopausal year, with less than 20 per cent achieving genuine, objective regression. Thereafter, although both androgens and estrogens became more effective with advancing age, the superiority of estrogens was apparent at every age-level. Overall, estrogens induced regression of disease in 36 per cent, and androgens in 21 per cent of postmenopausal women. Even if there were no difference, the distressing "side effects" of virilization would make the estrogens preferable.

The authors apparently refuse to concede any significance to a status of responsiveness following hormonal alterations, as compared to the nonresponsive patients. In most centers this is the basis for selection of patients for the major ablative procedures of hypophysectomy or adrenalectomy, although the latter is given no recognition in this article. Again, a cooperative study not under the aegis of CCNSC, involving 801 women treated by adrenalectomy, 390 by hypophysectomy, was retrospective and unrandomized, but—of more importance—the two series were shown to be biologically homogeneous (Surg., Gynec. & Obst., 115:215, 1962). Clearly demonstrated was the usefulness of reserving these ablative procedures for those patients already proven to be responsive to other hormonal measures. But the UC S.F. authors regard such an approach as "misleadingly optimistic," preferring to "determine the usefulness of hypophysectomy for an unselected population"—of 27 patients.

IAN MACDONALD, M.D.

The Author's Reply

THANK YOU for letting me see Dr. Ian Macdonald's letter on our article "Hormonal Treatment of Disseminated Cancer of the Female Breast," Calif. Med., 98:189, April, 1963. His letter has reached me in Cambridge, England where I am completing a sabbatical year's work on a mechanism by which breast cancer damages bone. Under these circumstances, it is not feasible to consult my co-authors or my colleagues in the Cooperative Breast Cancer Study Group under whose aegis the study was made and the report appeared. Accordingly, my comments reflect only my personal beliefs and are not necessarily those of the co-authors or of the Group.

Disseminated breast cancer is an important cause of morbidity and death and therefore a matter of public health concern. Naturally, I agree with Dr. Macdonald's implication that the proper time to cure the disease is before dissemination occurs. Unhappily, patients are often not seen until the disease is beyond surgical or roentgen eradication, as the quoted figures show. Some authorities go so far as to surmise that our best present treatment does not significantly alter the course of the disease. If true, this belief brings us to the biologic variability of the disease, a subject to which Dr. Macdonald has contributed significantly. He uses the term "biology" where others might say more simply that some tumors are indolent while others run a fulminating course. If this important variable were measurable, it could be randomized in our studies, just as we randomize the measurable variables of menopausal age and sites of metastasis. Our present scheme of randomization provides 12 categories. If only two types of biologic variation could be recognized, the number of categories would be doubled to 24. I agree that some of the visceral classifications are not comparable, e.g., a pleural effusion vs. brain metastases. Should we substitute pleural, lung, liver, brain and gastrointestinal metastases for visceral, increasing the variables fourfold and raising the number of categories to 96? As practical men, we are forced to compromise and trust that adequate numbers will result in comparable groups with respect to biologic variation and specific sites. Dr. Macdonald thinks our numbers too small. In fact, groups of 20 patients at our Clinic appear adequate, if only minimally so. Table 1 shows that the results of the completed University of California (San Francisco) studies closely parallel the combined national figures. Studies in 31 such Centers indicate that, using testosterone proprionate 300 mg/week as a reference standard (with its 20 per cent regression rate), groups of 20 randomized patients are sufficient to show if a compound is significantly less effective than testosterone propionate at the 95 per cent confidence level. Nonetheless, I agree with Dr. Macdonald that I should like to see our groups expanded and one of the purposes of our report is to acquaint physicians with the program at our Breast Tumor Clinic in the hope that they will refer their patients to it.

Dr. Macdonald's criticism of statistical evaluation is, in my opinion, retrogressive. Surely it is mathematically impossible to calculate a standard deviation on one regression in any number of cases, and no deviation is reported in the group to which he appears to refer (Table 3, Group G.). We do report means and on larger groups qualify these with

standard deviations so that the reader may know their variability and approximate significance.

The word "bias" has connotations other than statistical and appears to convey a pejorative meaning in Dr. Macdonald's reference to the bulk of data on androgens in the National Study. Like Dr. Macdonald, I greatly dislike using androgens in these women because of the cruel masculinization conventional androgens produce. Incidentally, this is not, as stated, a "side effect" but the physiologic action of the male hormone. One of the valuable results of the CCNSC study is the identification of progressively less androgenic derivatives *without loss of antitumor efficacy*, by protocol studies of 2-alpha-methyldihydrotestosterone (and its proprionate) and the completely non-androgenic compound, delta-one-testololactone. Would Dr. Macdonald have been willing to use estrogens, for which he seems to indicate a preference, as reference standards when the protocol was introduced, in view of the then general belief that estrogens accelerate disseminated breast cancer in women less than five years past the menopause? I would not, either ethically or forensically. The present cooperative study on stilbestrol vs. testosterone propionate has been set up in such a fashion that it should indicate whether estrogen can be used safely as a reference standard. Personally, I hope so. The non-androgenic delta-one-testololactone may also serve this function and, in fact, be preferable since it is less likely to cause nausea, vomiting, fluid retention, stress incontinence and uterine bleeding. I am sorry Dr. Macdonald confused the 18 per cent regressions from *primary* stilbestrol treatment with the 4 per cent figure for *secondary* treatment. The 18 per cent figure seems in accord with his bias for estrogens. It was to indicate our interpretation that stilbestrol and testosterone propionate have essentially similar antitumor efficacy that we presented what Dr. Macdonald calls our "fragmentary bit of information." I consider these data pertinent and the present cooperative study on the antitumor efficacy of stilbestrol vs. that of testosterone propionate essential in view of the lack of adequate "objective, controlled, randomized, reviewed data" on this subject.

I am truly sorry Dr. Macdonald thinks we "took a crack" at the A.M.A. study. We tried to indicate both here and in other publications our very great debt to that "pioneer study" (our expression). It taught us a lot: to set up prospective, randomized groups of comparable age and metastatic involvement, to include all patients entered into the study, to have extramural examiners review all films, photographs and measurements without knowledge of the treatment used, to use simple report forms, and, perhaps most important, that doctors genuinely interested in obtaining statistically adequate data can do so by pooling their individual experience, which must, of course, be acquired under identical conditions (outlined by the protocol). But then Dr. Macdonald again becomes ambivalent and criticizes us for selecting only one of several possible criticisms of the A.M.A. report. Surely, if the estrogen-treated group is 20 years older than the androgen-treated group, and therefore much more likely to obtain regressions for that reason alone, it is not necessary to mention that half the androgens given were either less effective than testosterone propionate or given in less than the optimal dose of 300 mg a week, that half of the cases had to be dropped from the report, and that random statistics were applied to selected data. It was not and is not our purpose to publish a detailed analysis of the shortcomings of the A.M.A. report. After all, it was made very early in the history of cooperative studies and can properly, I believe, be characterized as a "pioneer study." I cannot agree that the criteria of that study, at least as published, were more stringent than those of the present, or CCNSC, study. The lack of randomization, which Dr. Macdonald appears to think unimportant in the A.M.A. study, means that incomparable groups were compared. The present protocol has its faults, but it does remarkably well, in my opinion, particularly when one considers that it is accepted by 31 groups of clinical investigators, a population not known for its acceptance of regimentation.

Why Dr. Macdonald introduces the matter of the comparative antitumor efficacy of adrenalectomy and of hypophysectomy to a discussion of our report is not clear to me. I agree that the report he cites shows that the two procedures yield comparable regression rates. But if the rates can be compared with each other, they cannot be applied to the large population of women with advanced breast cancer since the reported data are derived, for the most part, from the selected minority of patients whose disease had previously responded to castration or hormones. Our data seem to indicate that in unselected women with far advanced breast cancer, innocuous substitution therapy alone yields twice the regression rate of hypophysectomy. Under these circumstances, for my part, 27 hypophysectomies is quite enough. This study was, in my opinion, necessary to test the hypothesis Dr. Macdonald advances in view of selection in previous series. I am pleased to find that our data seem to support his belief, and I therefore agree that the proper place of ablative procedures is restricted to young women whose disease has responded favorably to castration and/or hormones, and is once again progressing.

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